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| 10/575,827 | 04/14/2006 | Ernst Kusters | 33395-US-PCT | 6756 |

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ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

| EXAMINER | |
|---|---|
| KLINKEL, KORTNEY L | |
| ART UNIT | PAPER NUMBER |
| 1611 | |
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| 11/17/2011 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/575,827 | KUSTERS ET AL. | |
| | Examiner | Art Unit | |
| | Kortney L. Klinkel | 1611 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 September 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6 and 9-16* is/are pending in the application.

4a) Of the above claim(s) *3,4,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 6 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/8/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Acknowledgement is made of the remarks/amendments filed 9/8/2011. Claims 1-4, 13 and 16 were amended. Claims 5, and 7-8 stand cancelled. Claims 1-4, 6,and 9-16 are pending. Claims 3-4 and 9-10 remain withdrawn for being directed to nonelected subject matter. Claims 1-2, 6, and 11-16 are under consideration to their full extent. The species election is withdrawn.

The Examiner notes claims 3 and 4 are labeled "Withdrawn-previously amended". However, they should have been labeled "Withdrawn-currently amended" as there are current amendments shown in the claims.

### *Information Disclosure Statement*

Acknowledgement is made of applicant's submitting an information disclosure statement on 9/8/2001. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

### *Claim Objections—Withdrawn*

The objection of claims 1 and 2 because of informalities is withdrawn in light of the claim amendments.

### *Claim Rejections - 35 USC § 112—Withdrawn*

The rejection of claims 1, 6, and 11-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the claim amendments.

### *Claim Rejections - 35 USC § 112 4th Paragraph—Withdrawn*

The rejection of claim 2 under 35 USC § 112 4th Paragraph as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in light of the claim amendments.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

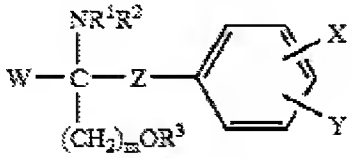
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 6 and 11-16 are rejected under 35 U.S.C. 103(a) as being obvious over Chiba et al. (US 6004565). This rejection is maintained.

Chiba et al. teach compounds of the following generic structure (col. 3, line 44-col 4. line 40) which are useful as immunosuppressants:




Wherein W is C1-6 alkyl substituted optionally substituted by hydroxy, *inter alia*, m is 1-3, R1, R2 and R3 are hydrogen, alkyl or acyl, X is a straight-chain alkyl having p number of carbons, or the straight chain alkyl may have 1-3 substituents including phenyl which may have 1-3 substituents including alkyl *inter alia*, Y is alkyl, *inter alia* and Z is a straight-chain alkylene having q number of carbon atoms. Variables p and q are the same or different and each is an integer of 1 to 20 with the proviso that p + q is between and including 6 and 23. In summary, the generic structure of Chiba et al.

encompasses the instantly claimed compounds. The Examiner acknowledges that the definition of W of Chiba et al. (col. 3, lines 57-61) is somewhat ambiguous. This section states "or a straight or branched chain C1-C6 alkyl substituted by 1 to 3 substituents selected from the group consisting of a halogen, a cycloalkyl, and a phenyl, which may be substituted by hydroxy." It is unclear what exactly may be substituted by hydroxyl. It is the position of the examiner that the C1-C6 alkyl chain may be substituted by hydroxy. This position is supported by the fact that exemplified compound FTY720 (col. 5, lines 1-8) has W equal to hydroxymethyl, or a C1 alkyl substituted by hydroxy. It is further noted that compound FTY720 has the same amino-1,3-diol head group as required by the most specific claim, claim 16, as well as a C8 alkyl chain para to this head group as required by instant claims 2, 13 and 16. Compound FTY720 differs from the compounds of the instant claims in that the R6 substitution of the instant claims is missing from this compound. However, Chiba et al. teach that in addition to X being H (as in FTY720), that X can be a straight chain alkyl substituted with phenyl, which may also be substituted with alkyl (col. 3 line 63-col. 4 line 7).

Chiba also teaches a pharmaceutical composition comprising said compounds in association with a pharmaceutically acceptable diluent or carrier (column 8, lines 19-28).

Chiba et al. generically teach compounds encompassing the instantly claimed compounds, but fail to teach a specific example of a compound falling within the claimed genera.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at the compounds of the instant claims, including a compound wherein R1 is ethylene, R2 is octyl and in the para position relative to R1, R5 is hydrogen and R6 is 4-octylphenylethyl in the meta position relative to R1 (note the 112 2nd rejection above regarding the relative position of the substituents) based on the teachings of Chiba et al. with a reasonable expectation for success. One would have been motivated to do so because Chiba teaches a generic structure consisting of a finite number of compounds that fully encompasses the elected species which are useful as immunosuppressants, which is the same utility disclosed for the claimed compounds. In addition to the generic immunosuppressant compounds disclosed by Chiba et al.,Chiba et al. teach compound FTY720 having the same core structure required by the most specific claim, claim 16. It would have been obvious to one of ordinary skill in the art to replace the X equal to H of FTY720, with a straight chain alkyl substituted with phenyl, which may also be substituted with alkyl, specifically 4-octylphenylethyl given the fact that this group is taught to be an acceptable X substituent.

Applicant's data in the specification has been considered. The specification states at page 6 that the compounds of formula I exhibit valuable pharmacological properties such as agonism of S1P receptors as indicated by in vitro and in vivo tests. The specification then outlines various in vitro and in vivo tests and then state that compound of formula I deplete peripheral blood lymphocytes when administered at a dose of 0.03 to 3 mg/kg. There are no specific results for individual compounds. There

is no indication from the specification that the compounds of the instant claims exhibit superior or somehow unexpected immunosuppressant activity greater than those expected based on the teachings of Chiba et al.

***Response to Arguments***

Applicant's arguments filed 9/8/2011 in response to the rejected claims have been fully considered, but are not persuasive.

Applicant argues that the compounds of claim 1 do not fall within the scope of the cyclic genus of compounds described by Chiba because the definition of W does not include hydroxymethyl or any hydroxyalkyl group. Applicant argues that the plain English meaning of the W substituents definition "or a straight or branched chain $C_1$-$C_6$ alkyl substituted by 1-3 substituents selected from the group consisting of a halogen, a cycloalkyl and a phenyl, which may be substituted by hydroxy:" is that hydroxy can only be a substituent on a substituent on the straight or branched chain $C_1$-$C_6$ alkyl group. This argument has been fully considered, but is not persuasive.

As discussed in the above rejection, the Examiner acknowledges that the description of Chiba et al. for the W substituent is somewhat ambiguous and may be read different ways. However, given the fact that the cyclic containing compound FTY720 has a head group wherein W is hydroxy methyl, it is clear that the generic description of W encompasses C1-C6 alkyl substituted by hydroxy. Again it is pointed out that compound FTY720 contains the exact same di-methoxy amino head group as required by the most specific claim, instant claim 16. Additional support for the position that C1-C6 alkyl can be substituted by hydroxy stems from the fact that the different W

substituents listed by Chiba et al. are separated by semicolons. The entire phrase "or a straight or branched chain C1-C6 alkyl substituted by 1 to 3 substituents selected from the group consisting of a halogen, a cycloalkyl, and a phenyl, which may be substituted by hydroxy;" is one semicolon group. Any and all of the moieties therein can reasonably be substituted with hydroxy. This is a reasonable reading of the teachings of Chiba et al. especially given the fact that preferred compound FFTY720 has W being a C1-C6 alkyl substituted hydroxy. In reading Chiba et al. as a whole, one of ordinary skill in the art would come away knowing that 2-aminiopropane-1,3-diol head-group containing compounds are encompassed by the teachings therein. Note the first generic structure of the document on col. 3, lines 27-38. This generic structure also encompasses the claimed compounds and has the required 2-aminopropane-1,3-diol head-group.

Applicant argues that Chiba does not state or suggest that FTY720 is embraced within or in any way related to either of the two independent genera of ALH-immunosuppressants described in columns 3 and 4 of the reference. Applicant argues that one of skill in the art reading Chiba, would have no reason to associate FTY720 with either of the genera of compounds mentioned in column 3. This argument has been fully considered, but is not persuasive.

Preceding both generic structures, Chiba et al. use the phrase "In general, for this invention..." and "Also, for this invention..." likewise, regarding the introduction of preferred compound FTY720 Chiba et al. use the phrase "One preferred structural embodiment of the ALH-immunosuppressive compounds used in the invention is..." These statements, in combination with the entire disclosure of Chiba et al. make it clear

that compounds having the required 2-aminopropane-1,3-diol headgroup are contemplated for use as ALH-immunosuppressive compounds. The examiner also notes that the two generic structures and FTY720 are not all mutually exclusive. The two generic structures overlap in scope. Additionally the Examiner is of the position that FFTY720 falls within both generic structures.

Applicant argues that the Examiner's reference to the claims to support an interpretation of a prior art text is misplaced and is based entirely on hindsight and that the claims of the present application are not relevant to the meaning of any part of the Chiba disclosure. This argument has been fully considered but is not persuasive.

The Examiner in no way uses hindsight in the rejection. The Examiner makes reference to instant claim 16 only in stating that FTY720 has the same amino-1,3-diol head-group as claim 16--and because claim 16 is the most specific claim pending, this teaching necessarily means that FTY720 has the same head group as the other less specific claims. This statement was placed in the rejection in an effort to help illustrate exactly how the teachings of Chiba et al. read on the instant claims.

Applicant also argues that one of skill in the art of organic chemistry or pharmaceutical chemistry reading Chiba would not conceive of the presently claimed compounds with any expectation, let alone a reasonable expectation, that they would be active as ALH-immunosuppressive compounds. Applicant argues that FTY720 is the only ALH-immunosuppressive compound specified by Chiba and is the preferred compound of Chiba. These arguments have been fully considered, but are not persuasive.

Chiba et al. teach that the entire genus of compounds having the structure shown in the above rejection (also Chiba col. 3 lines 44-col. 4 line 40) are expected to have ALH-immunosuppressive activity. Applicant has not provided evidence to the contrary. The fact that compound FTY720 is the preferred compound and the subject of the working examples of Chiba does not detract from the fact that Chiba clearly teaches that all the compounds encompassed by the generic structure would be expected to have ALH-immunosuppressive activity. Again it is noted that the instant specification discloses this same activity for the instantly claimed compounds. Applicant has not provided evidence of unexpected results for the claimed compounds over the teachings of Chiba. Again the Examiner highlights the fact that FTY720 only differs from the claimed compounds in the nature of the benzene ring substitutions and the generic teachings of Chiba et al. supply this missing piece.

## ***Conclusion***

Claims 1-2, 6, and 11-16 are rejected. No claim is allowed.

No new ground(s) of rejection were presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kortney Klinkel, whose telephone number is (571)270-5239. The examiner can normally be reached on Monday-Friday 10 am to 7 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KLK

/Joanne Hama/
Primary Examiner, Art Unit 1632